Withdrawal of parenteral phenobarbitone – implications for resource-poor countries

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Parenteral phenobarbitone is an integral part of the management of status epilepticus, especially in the context of resource-poor countries. It is highly effective at controlling seizures. It is safe, cheap, can be given by rapid intravenous push or intramuscular route, boluses can be repeated, and it is recommended as part of the Advanced Paediatric Life Support guidelines. The proposed alternatives lack efficacy, practicality and/or place the child in status epilepticus at risk of respiratory compromise. The impact of the loss of parenteral phenobarbitone would be increased cardiac complications, lack of early seizure control, prolonged seizures resulting in brain damage and systemic complications. Increased numbers of patients will require artificial ventilation in centres without facilities, and centres with facilities will be unable to cope with the load of ventilated patients because of lack of safe transport systems and bed space.

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Status epilepticus in childhood is a common medical emergency requiring swift and effective termination in order to limit subsequent adverse complications. Parenteral phenobarbitone is the main agent used in most centres to attain this.

The production of parenteral phenobarbitone in South Africa stopped in December 2004; this was a worldwide policy by the suppliers.

Phenobarbitone is recommended in the most recent Advanced Paediatric Life Support (APLS) guidelines (Fig. 1).[1] Its withdrawal has even more serious repercussions for the management of status epilepticus in resource-poor countries (RPCs).

Phenobarbitone can be administered by slow intravenous push or intramuscularly, a route that is often used in RPCs.[2,3] It is an effective agent for the control of status epilepticus.[4,5] Side-effects are respiratory depression and lowering of blood pressure, the underlying disease being the main related factor and the rate of rise of serum levels.[6] Accordingly it can be and is used at all levels of hospital care. The authors concur with the APLS guidelines and have recommended the use of phenobarbitone for the third line of treatment for the management of status epilepticus in RPCs (Fig. 2).[7,8]

If the supply of parenteral phenobarbitone terminates, the alternatives for our setting are limited. Lorazepam or other benzodiazepines are associated with increased risk of respiratory depression[9] and the risk will increase where benzodiazepines are already used as first-line treatment.

Phenytoin is the alternative agent to phenobarbitone in the APLS algorithm. Intravenous phenytoin is associated with fatal haemodynamic complications, serious skin reactions at the injection site and cardiac arrhythmias.[10] The agent should be administered into a large vein (but ideally not central), via a slow infusion over 30 minutes through a syringe driver. The child should have cardiac monitoring. These facilities for safe administration are often not available in hospitals in RPCs. Following the guidelines, the administration of phenytoin takes three times as long as the slow push of phenobarbitone. The delayed time to administer therapy may increase the risk of refractory status epilepticus, which is associated with subsequent brain damage.[11] Furthermore, the APLS guidelines recommend measuring levels 60 - 90 minutes after completion of the infusion, but this is only available in a few tertiary or research centres in RPCs. Although more economical than the newer anticonvulsants, parenteral phenytoin is still four times the cost of phenobarbitone. In addition, it is not as fast or effective at controlling status epilepticus as phenobarbitone.[4,5,12,13]

In conclusion, although pharmaceutical companies may not make substantial profits from the manufacture of phenobarbitone, withdrawal of this drug is likely to have a devastating effect on the outcome of status epilepticus in RPCs. Currently various bodies are attempting to ensure that this agent remains available in South Africa. This crisis should be viewed as an example of the potential dependency of the medical profession on drug company policy, and the latter's potentially catastrophic effects on the care of our patients.

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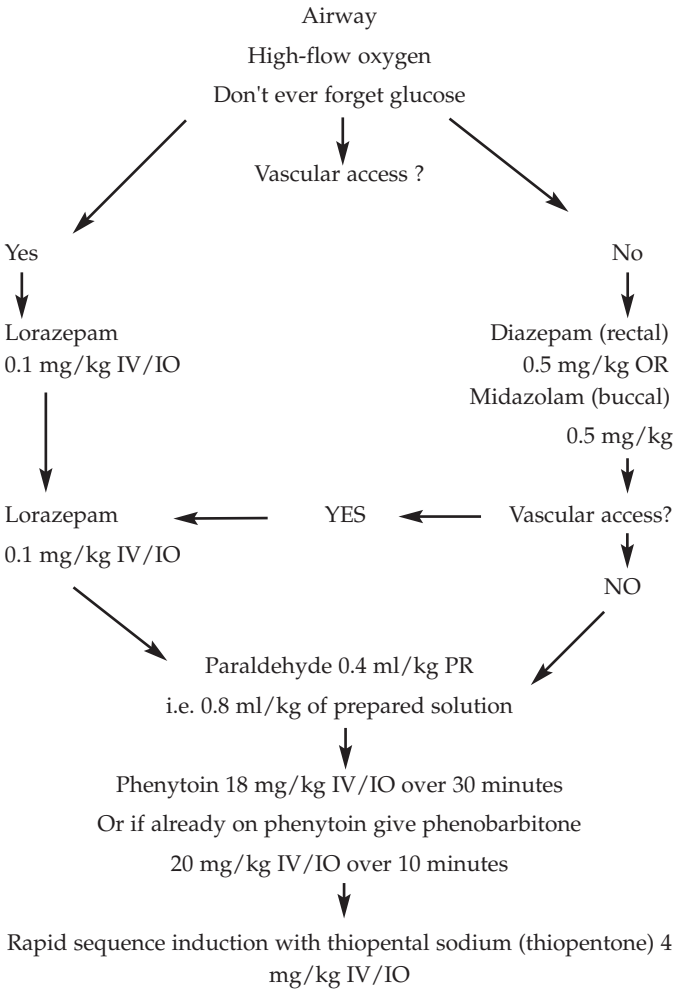
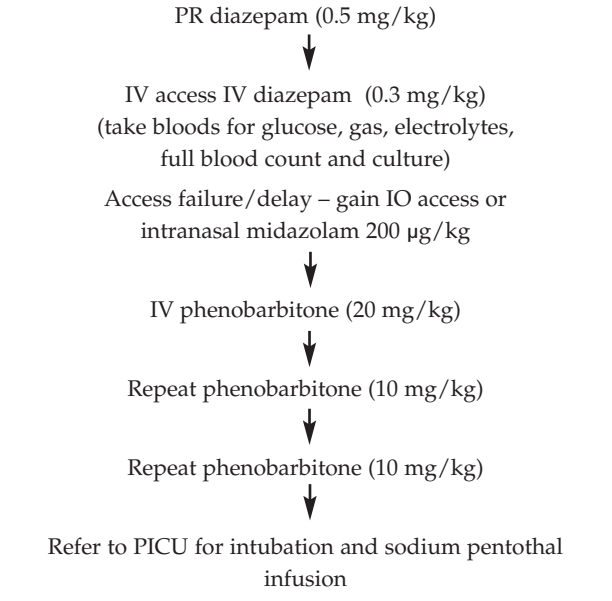


Fig. 1. APLS status epilepticus algorithm (2005)[1] *(IV = intravenous; IO = intra-osseous; PR = per rectum).*



Alternatives: (*i*) lorazepam (0.1 mg/kg), a faster-acting alternative to diazepam for bolus IV intervention; (*ii*) midazolam intranasally (200 µg/kg) or sublingually (500 µg/kg) if there is no venous access; (*iii*) midazolam infusion loading at 200 µg/kg by slow IV injection, then titrating an infusion between 30 µg/kg/h and 300 µg/kg/h – alternatively, clonazepam (Rivotril) infusion if seizure control is not gained after the first phenobarbitone infusion; (*iv*) phenytoin (20 mg/kg over 20 minutes) if there is known adverse reaction to phenobarbitone (monitor for cardiac arrhythmias); (*v*) watch carefully for drug-related respiratory depression; and (*vi*) intubation, ventilation and administration of sodium pentothal infusion should only be performed in a centre with trained anaesthetic and paediatric intensive care.

PR = per rectum; IV access = if IV access available; IO = intra-osseous; PICU = paediatric intensive care unit; ABCD = airway, breathing, circulation, drugs.

Fig. 2. Management of status epilepticus in South Africa[8] *– ABCD (oxygen, monitor saturation, pulse and blood pressure, glucose).*

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